

Supporting Information

Alternative syntheses of (S)-cEt-BNA – A key constrained nucleoside component of bioactive antisense gapmer sequences

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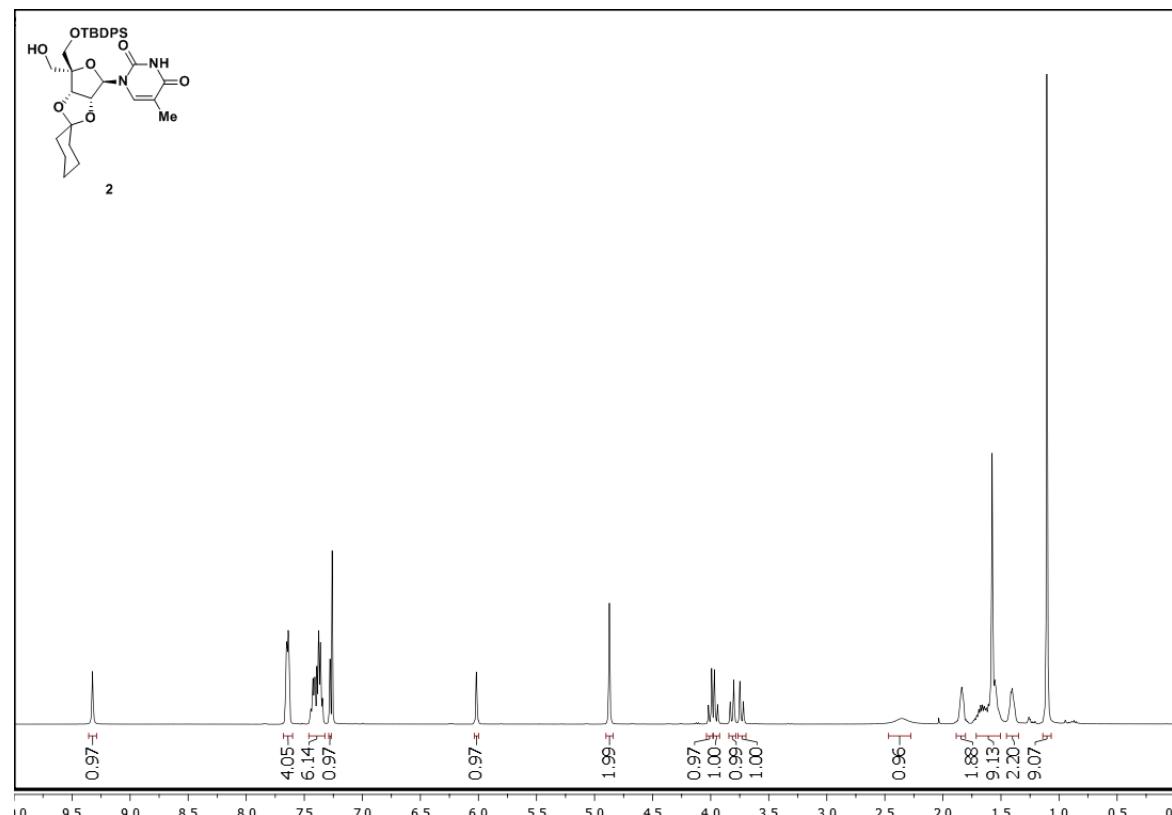
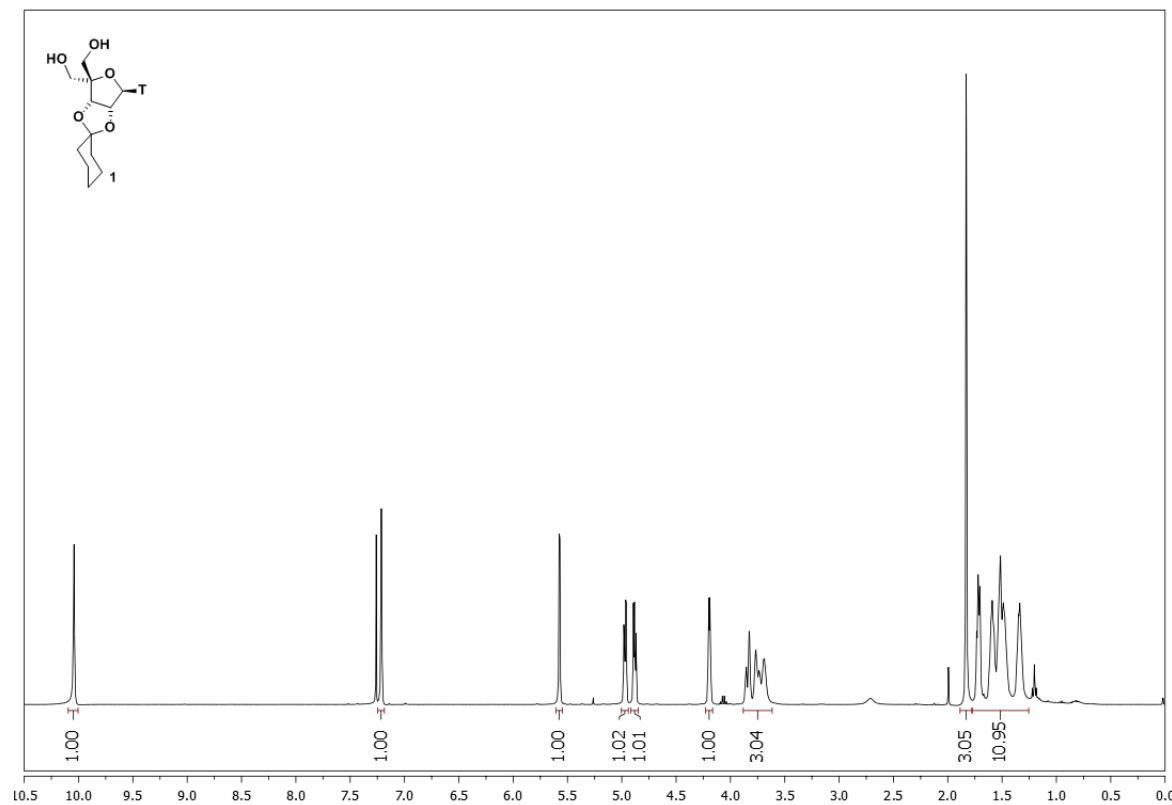
Table 1.....	SI 2
¹ H and ¹³ C spectra	SI 4

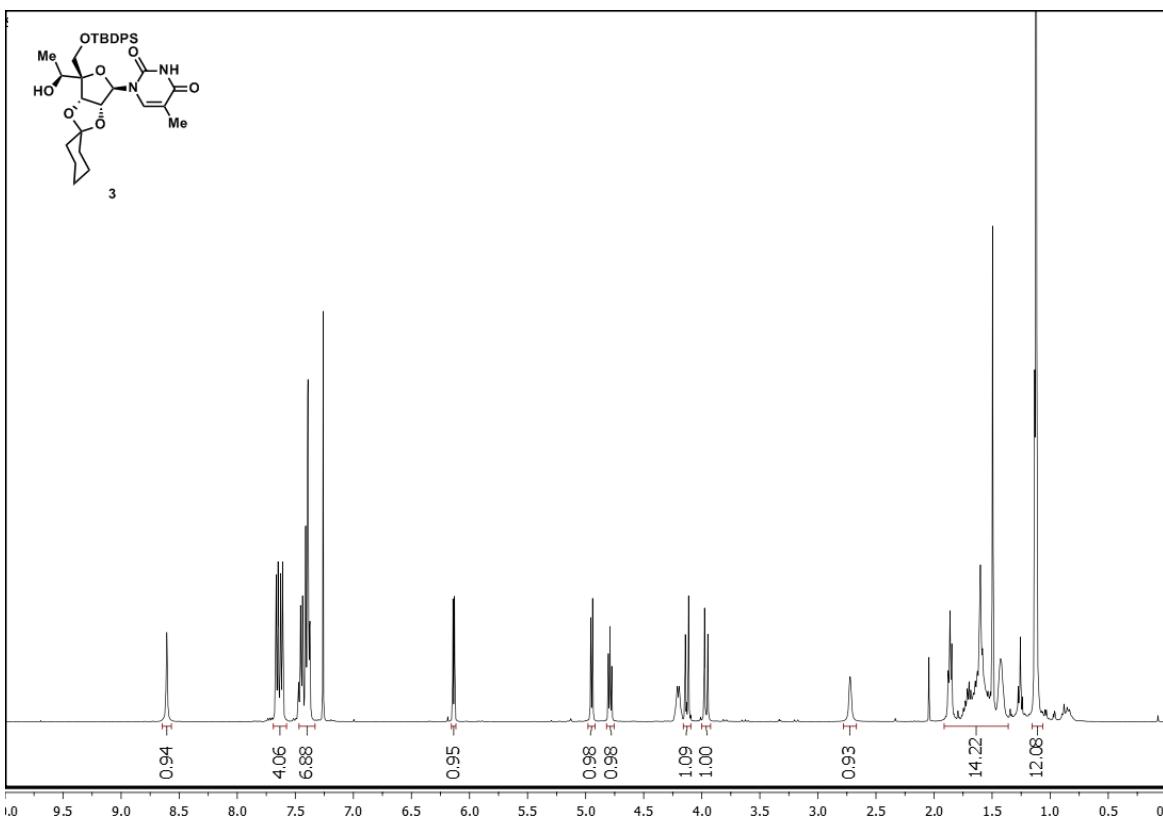
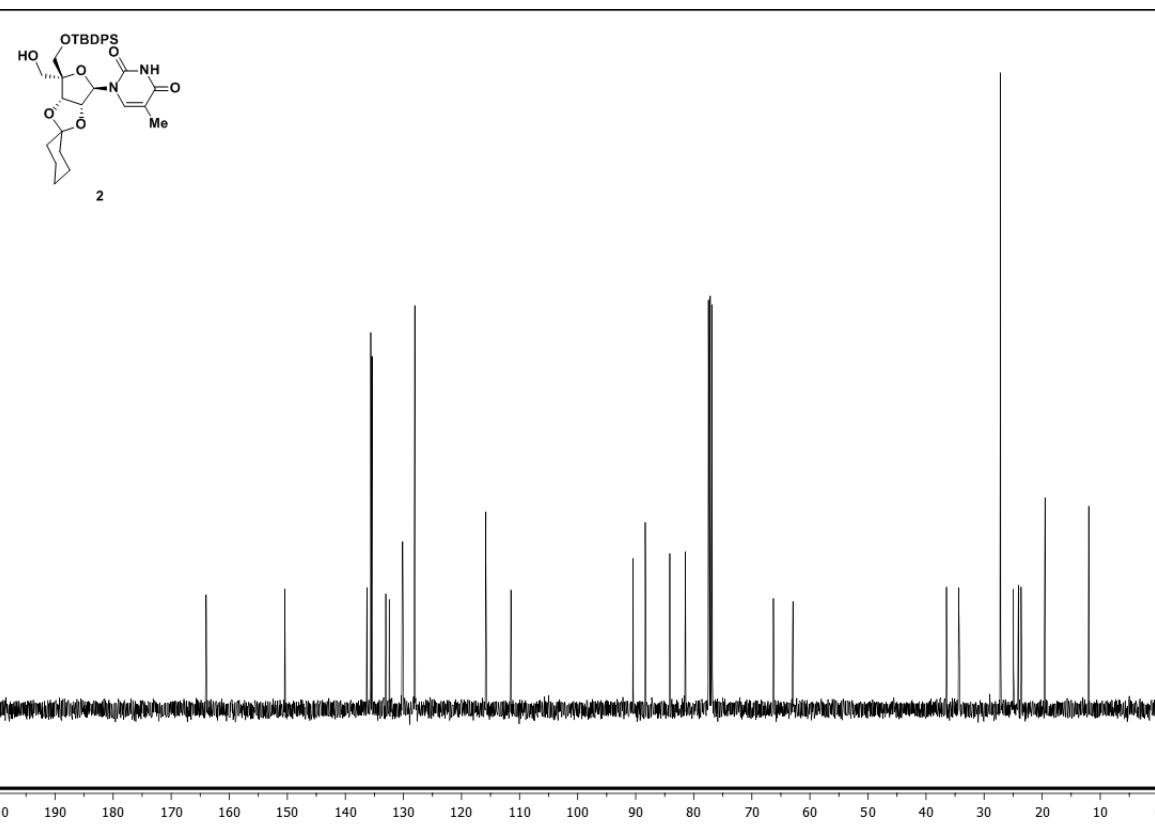
Table 1. Optimization of the key cyclization to produce **20** (Full version).

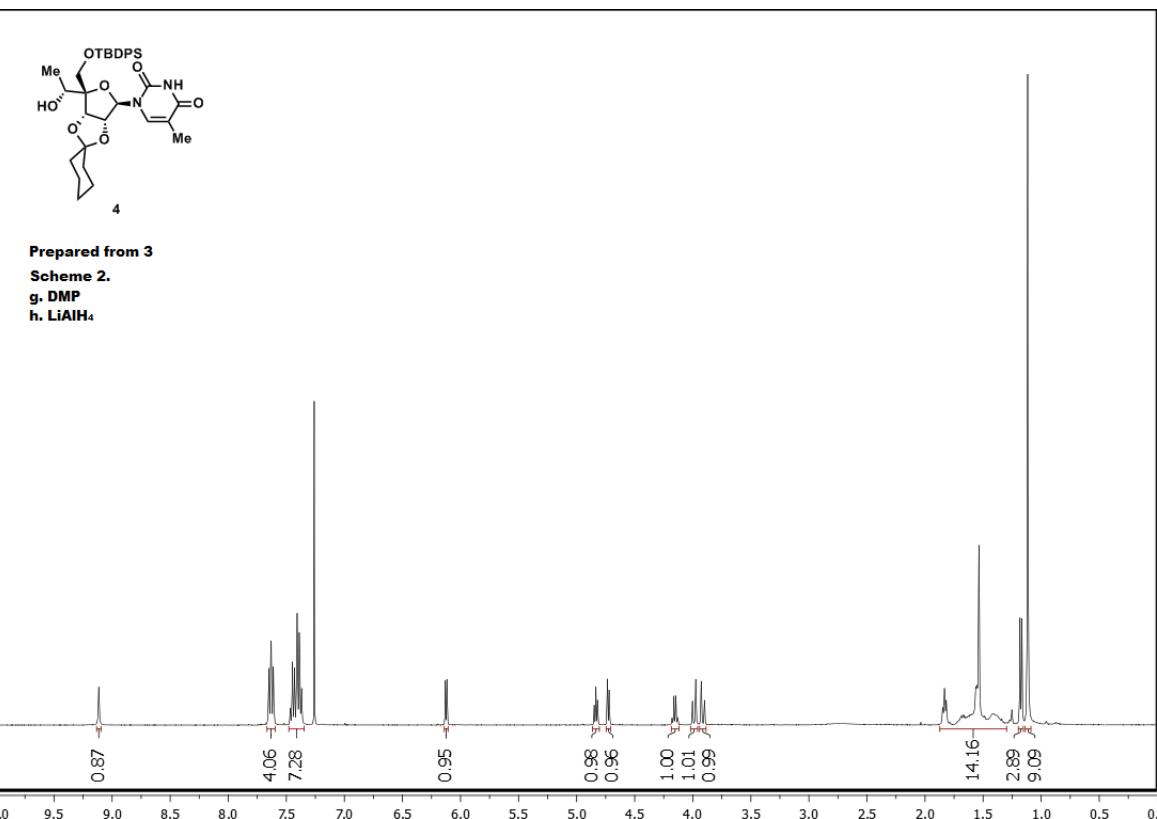
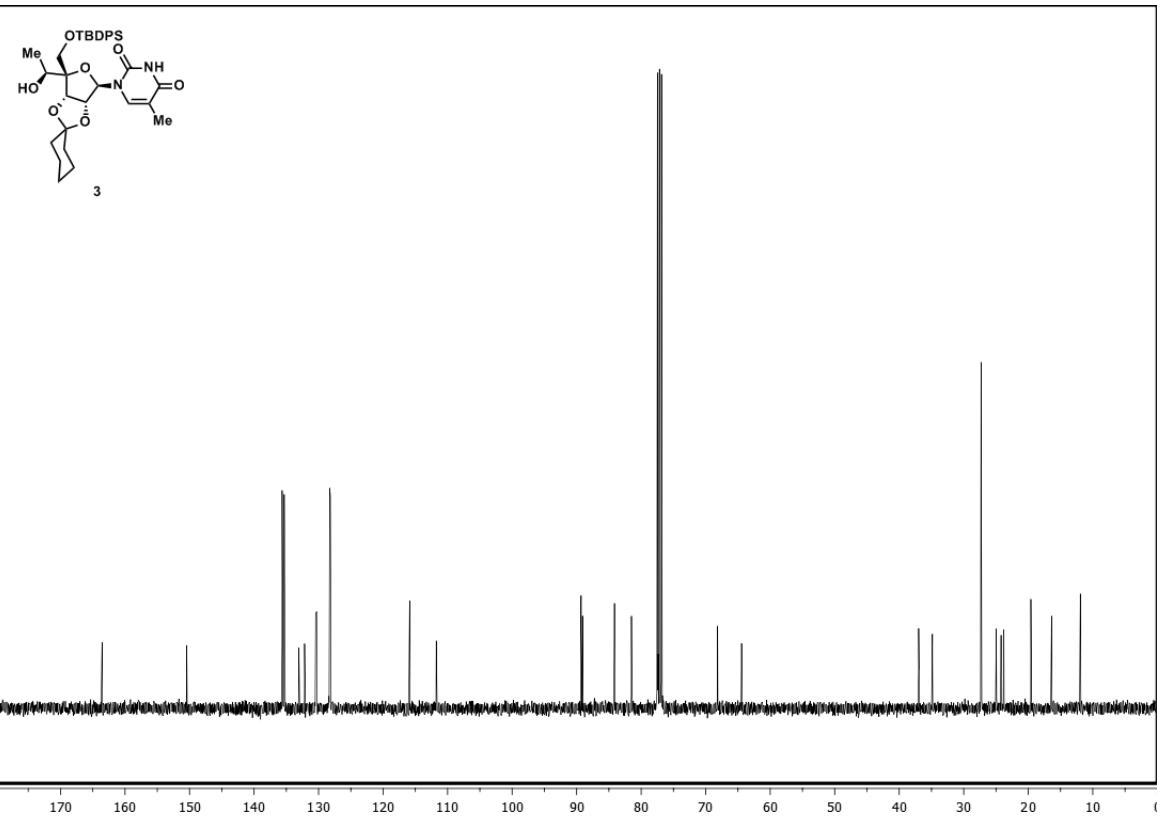
Entry	Condition	Ratio 6 : 20 : SM ^a
1	Potassium carbonate, MeCN	10:1:0
2	Pyridine, 80 °C, 3 days.	1:1.7:0
3	Pyridine, MgBr ₂ (2 equiv.), 80 °C,	3.7:1:0
4	Pyridine anhydrous, 80 °C, 24 h	1:1.8:12.5* 1:2.1:10*
5	Pyridine/H ₂ O 10:1, 80 °C, 20 h	1:1:1.2
6	Pyridine anhydrous, sealed tube, 120 °C, 20 h	1:1.6:0
7	2,6-lutidine (3 equiv.), toluene reflux, 24 h	2:1:0
8	2,2'-bipyridine (2 equiv.), toluene, 80 °C, 20 h	1:1:22
9	quinoline (2 equiv.), toluene, 80 °C, 20 h	1:0.9:5.6
10	phenanthridine (2 equiv.), toluene, 80 °C, 20 h	1:1.5:5.1
11	1,10-phenanthroline (2 equiv.), toluene, 80 °C, 20 h	1:2:2.6
12	DBU, dioxane	3.8:1:0
13	DBU (2 equiv.), toluene, 80 °C, 24 h	3.5:1:5
14	Triethylamine (2 equiv.), DMSO, 80 °C, 24 h	1.3:1:0.3
15	DIPEA (5 equiv.), toluene, 80 °C, 48 h	5:1:1
16	Imidazole (2 equiv.), toluene, 80 °C, 24 h	1:1:0
17	1-methylimidazole (2 equiv.), toluene, 80 °C, 24 h	3:1:10
18	2,2,6,6-tetramethylpiperidine (2 equiv.), toluene reflux, 48 h	2:1:0
19	1,5,7-Triazabicyclo[4.4.0]dec-5-ene (2 equiv.), toluene, 80 °C, 24 h	5:1:0
20	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (2 equiv.), toluene, 80 °C, 24 h	6.6:1:0
21	3,3,6,9,9-Pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene (2 equiv.), toluene, 80 °C, 24 h	6.6:1:0
22	(R,R)-N,N'-Bis(1-phenylethyl)guanidine (2 equiv.), toluene, 80 °C, 24 h	1.2:1:1.3
23	(R,R)-N,N'-Bis(1-phenylethyl)-2-imidazolidine (2 equiv.), toluene, 80 °C, 24 h	2.3:1:12.5

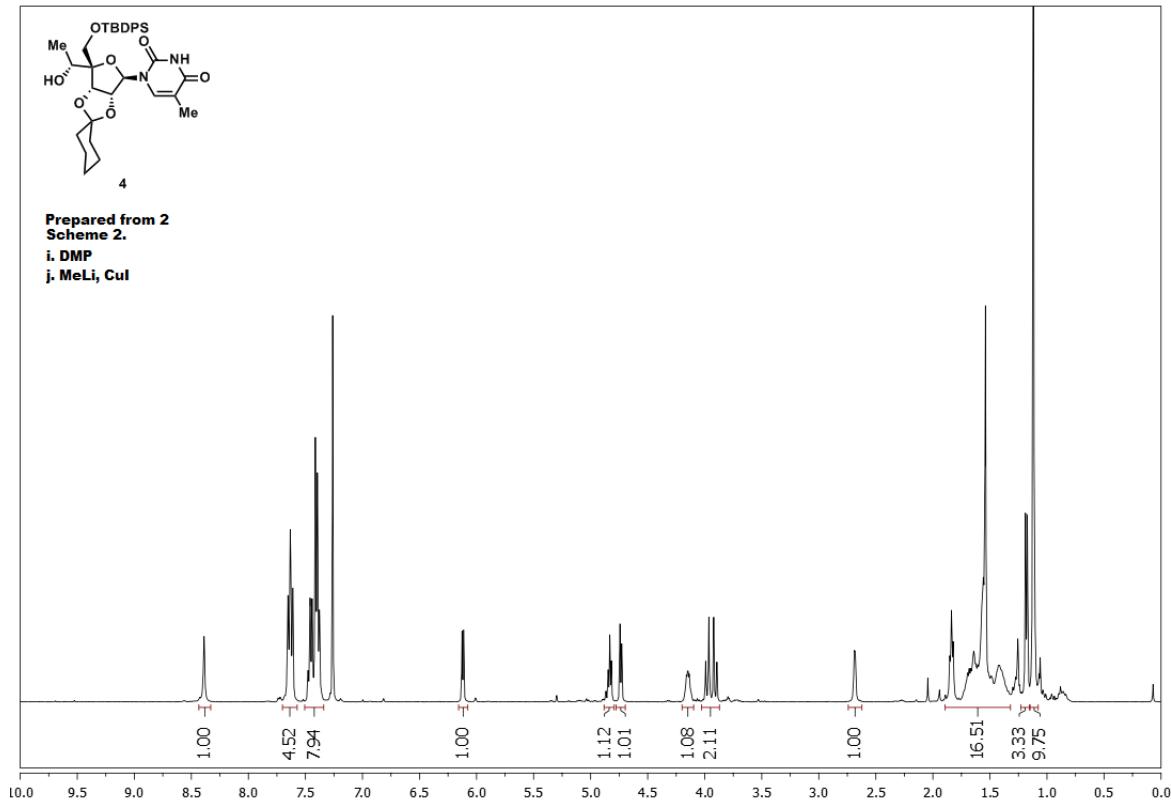
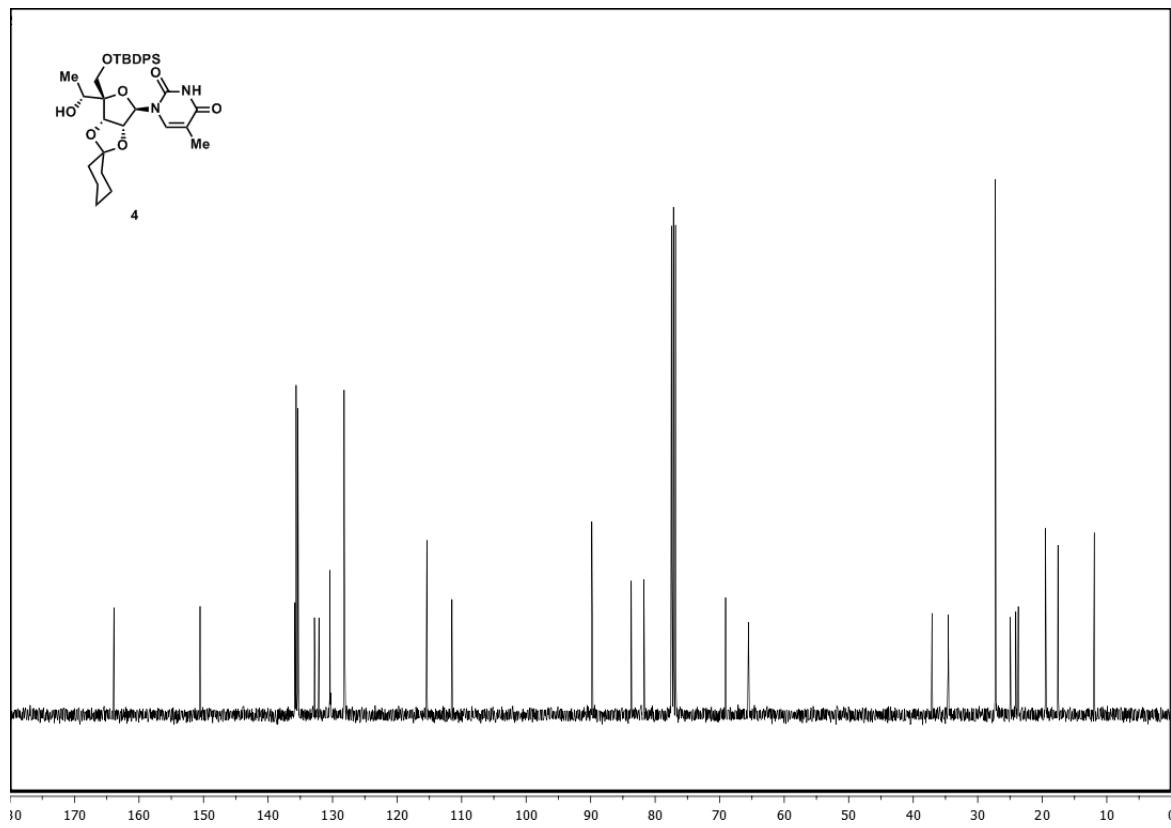
24	(S,E)-1-(naphthalen-1-yl)-N-(pyrrolidin-2-ylidene)ethanamine (1.5 equiv.), toluene, 80 °C, 24 h	Decomposition
25	(S,E)-1-(naphthalen-1-yl)-N-(piperidin-2-ylidene)ethanamine (1.5 equiv.), toluene, 80 °C, 24 h	1:1:8.5
26	BEMP, Toluene, rt, 36 h	>20:1:0
27	N-methylmorpholine (2 equiv.), toluene, 80 °C, 20 h	7:1:0
28	MgBr ₂ (2 equiv.), toluene, 80 °C, 20 h	6:1:0.8
29	LiBr (2 equiv.), toluene, 80 °C, 20 h	6.2 : 1 : 1.6
30	TBAOAc (2 equiv.), toluene, 80 °C, 20 h	3.4 : 1 : 0
31	Molecular sieves, toluene, 80 °C, 24 h	8.5:1:14*
32	Basic alumina, toluene, 80 °C, 20 h	1:1:4
33	Silica gel, toluene, 80 °C, 20 h	1:2.5:30*
34	DMF, 80 °C, 24 h	1.8:1:7.4*
35	dimethoxyethane, toluene, 80 °C, 24 h	No Rxn
36	N-methyl-2-pyrrolidone, 80 °C, 24 h	1:2.1:11*
37	DMSO, 80 °C, 24 h	1:2.7:1 1:2.6:5.7 (duplicate)
38	Methyl phenylsulfoxide (2 equiv.), toluene, 80 °C, 20 h	No Rxn
39	Dibenzyl sulfoxide (2 equiv.), toluene, 80 °C, 20 h	No Rxn
40	Methyl methylsulfinylmethyl sulfide (2 equiv.), toluene, 80 °C, 20 h	No Rxn
41	Methyl phenylsulfone (2 equiv.), toluene, 80 °C, 20 h	No Rxn
42	Sulfolane, 100 °C, 20 h	1:1:14*
43	HMPA, 100 °C, 20 h	1:3.6:0
44	DMPU, 100 °C, 20 h	1:1.1:0
45	DMI, 100 °C, 20 h	1:0.78:0
46	Water, 90 °C, 20 h	1:2.4:4.7
47	Pyridine, 110 °C, 36 h ^b	1:1:0

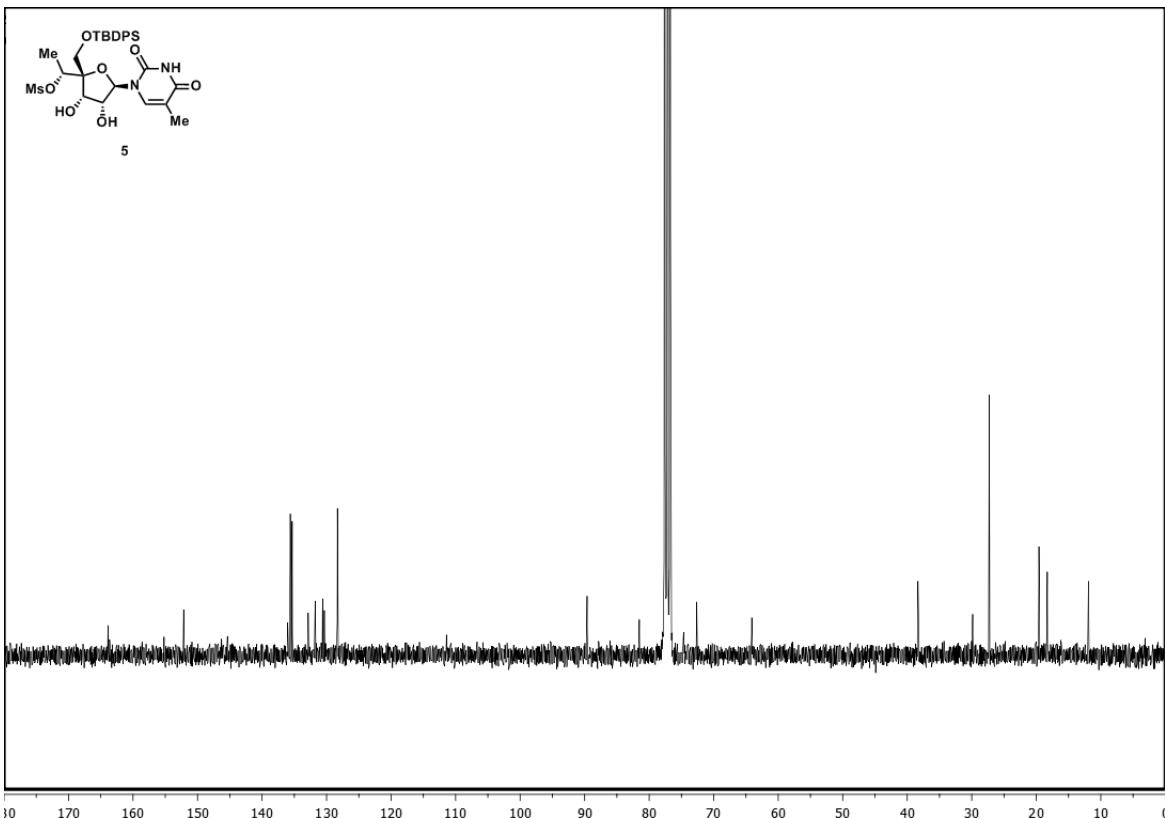
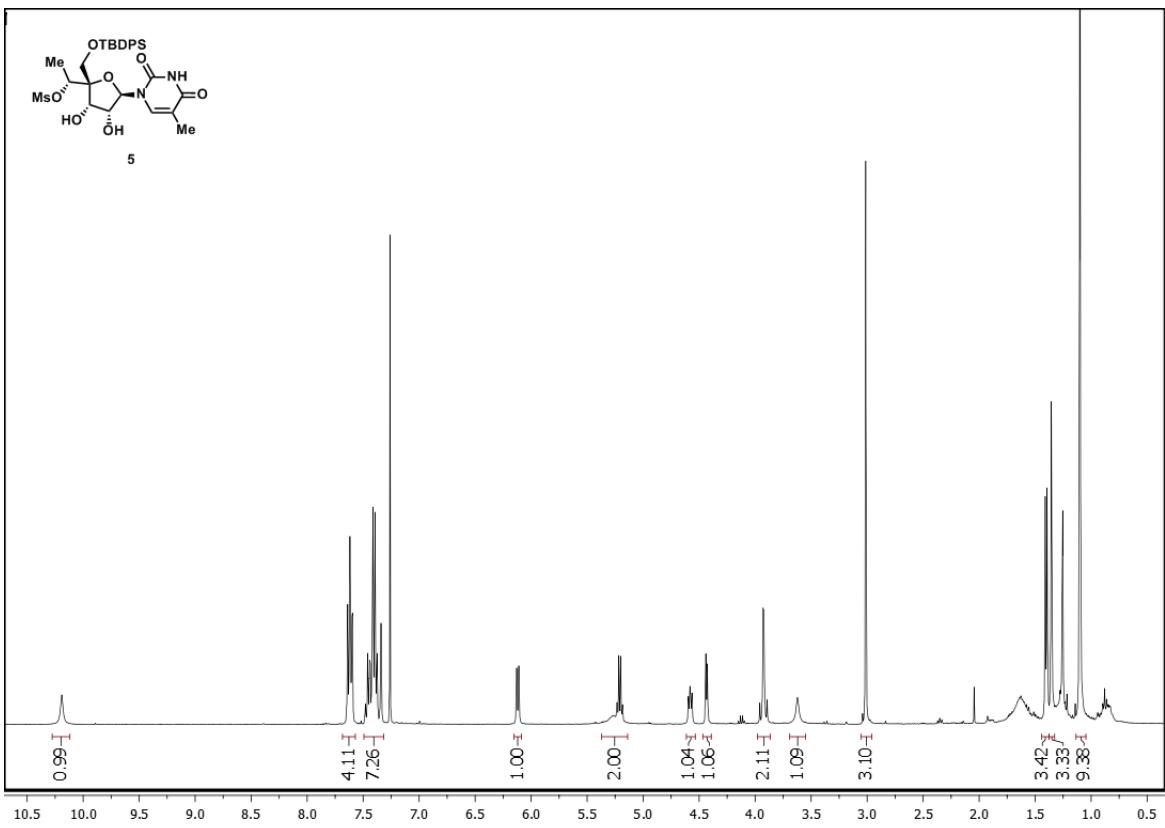
¹H and ¹³C Spectra

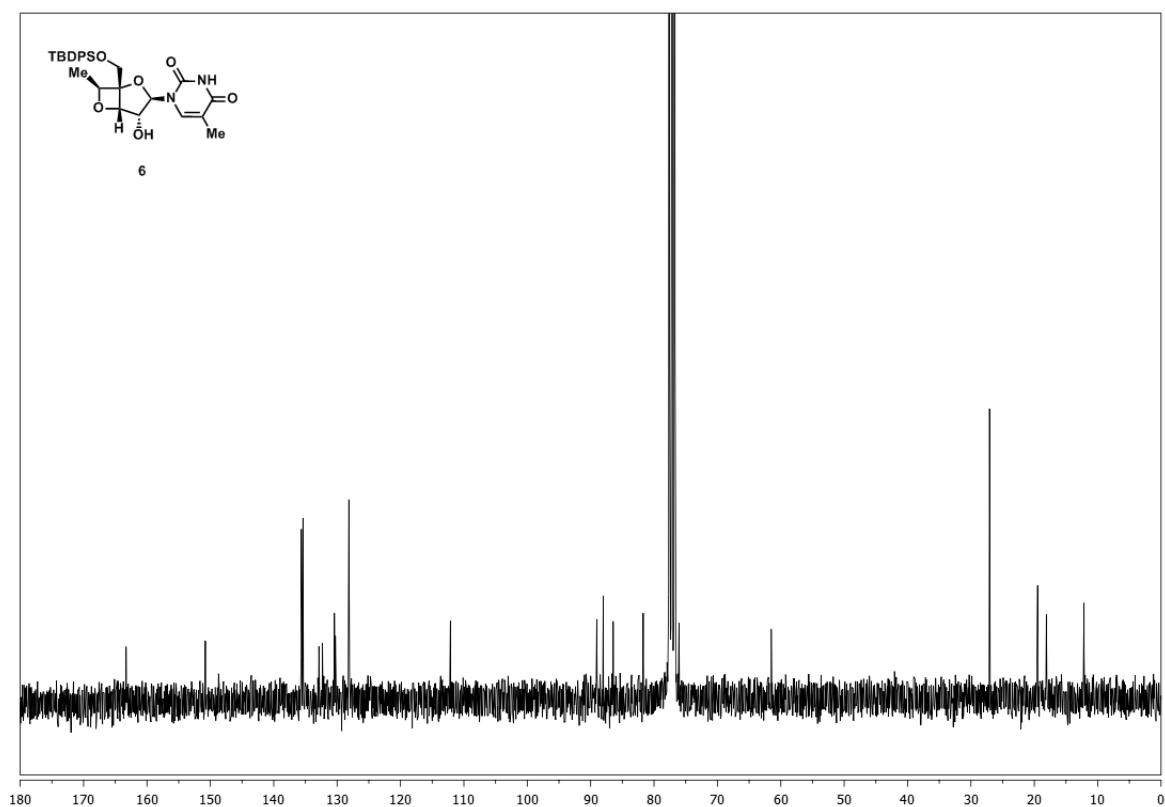
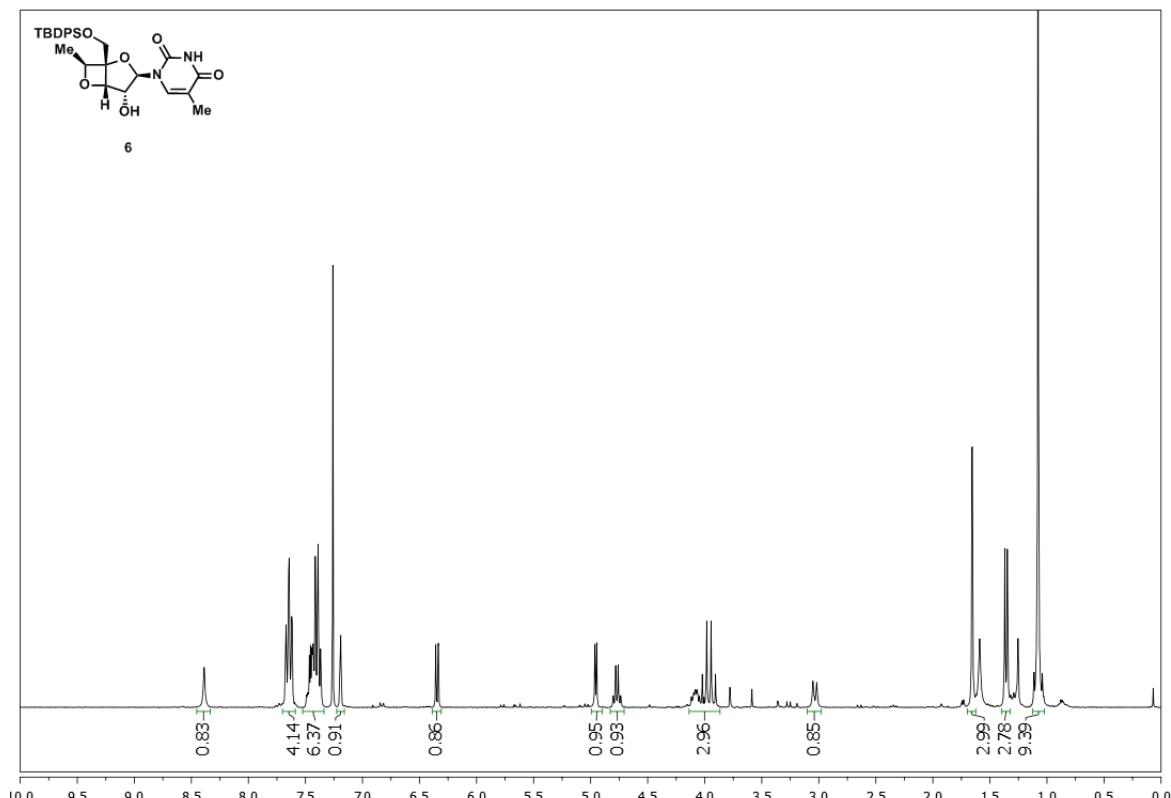


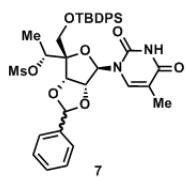




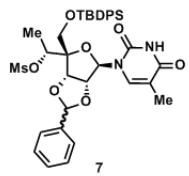
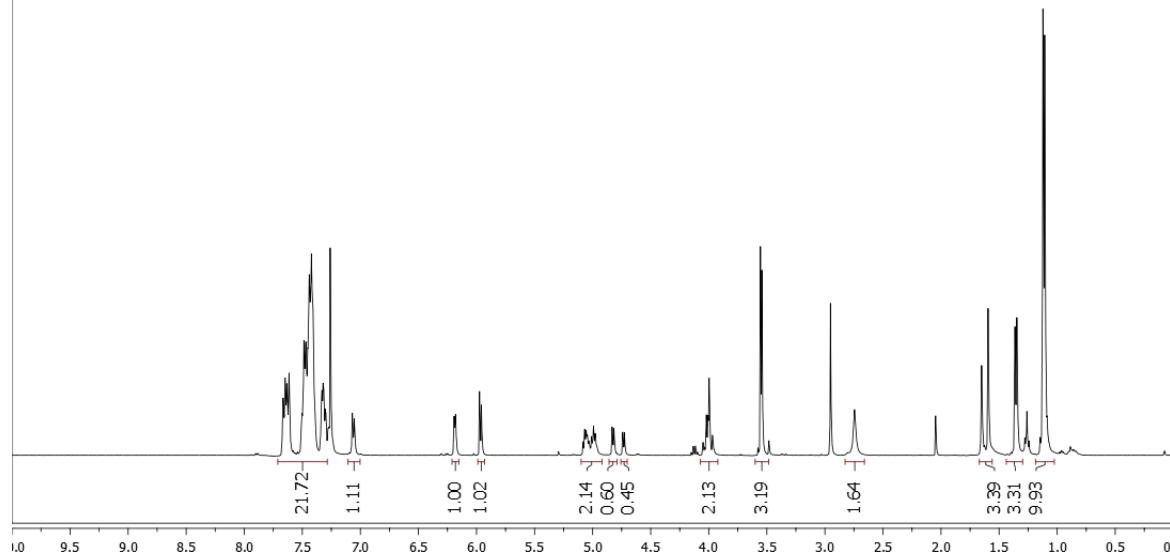




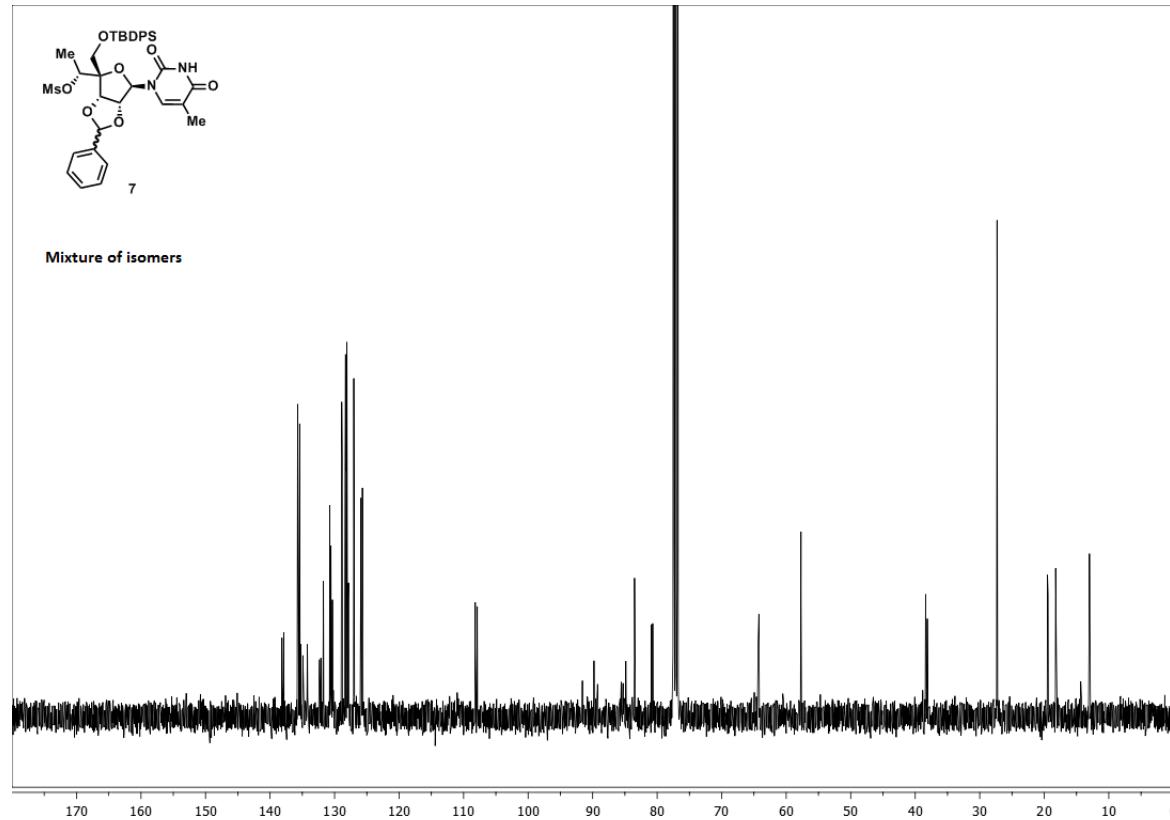


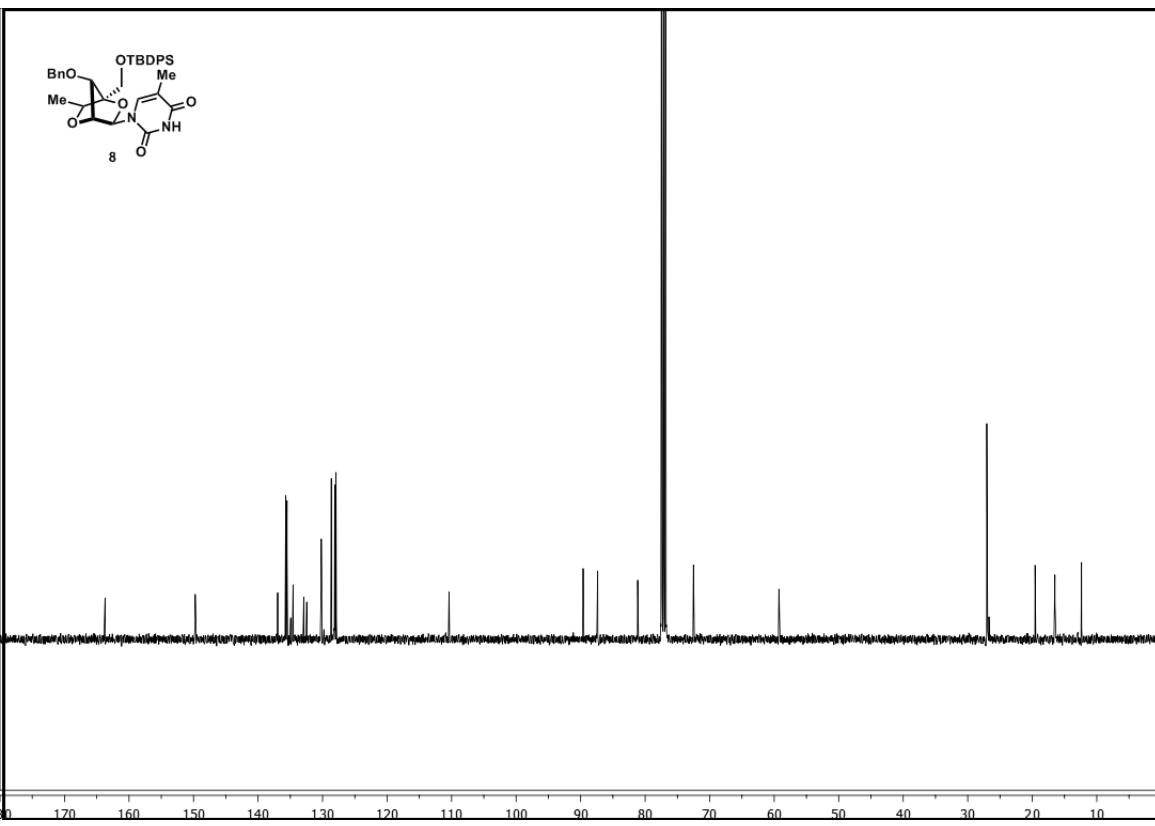
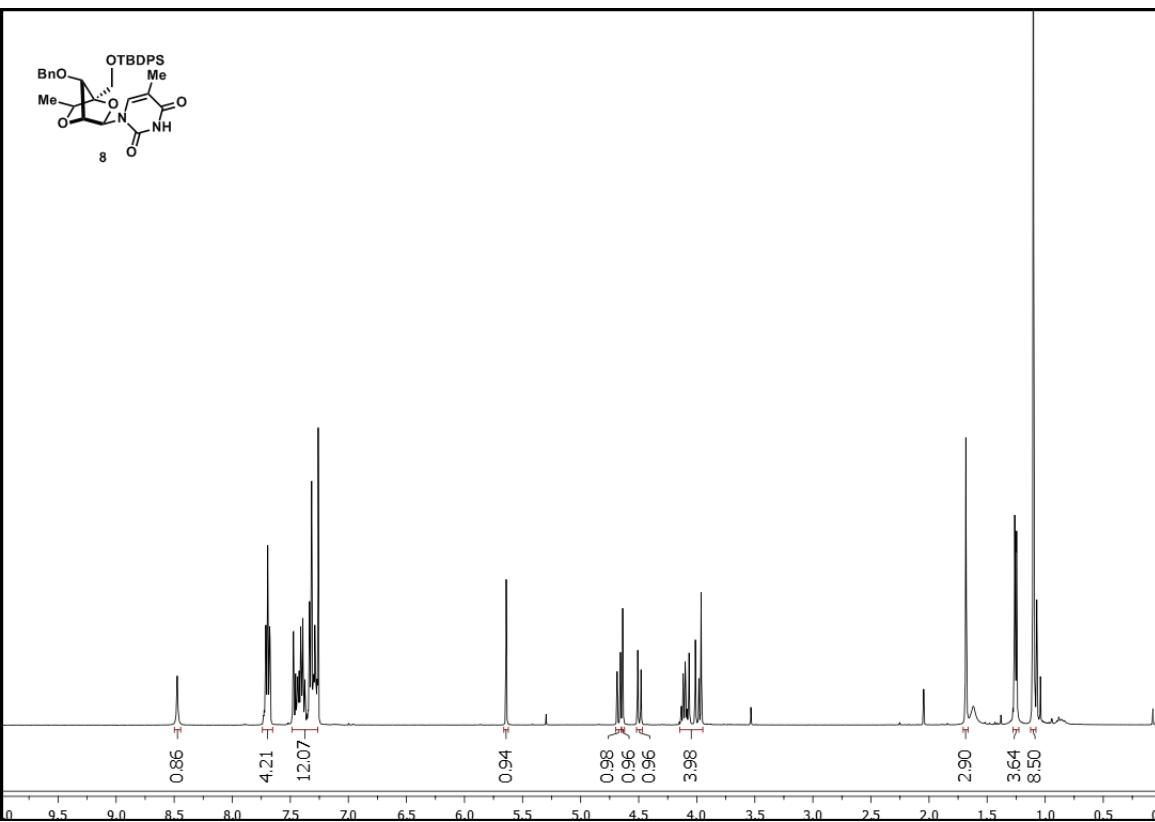


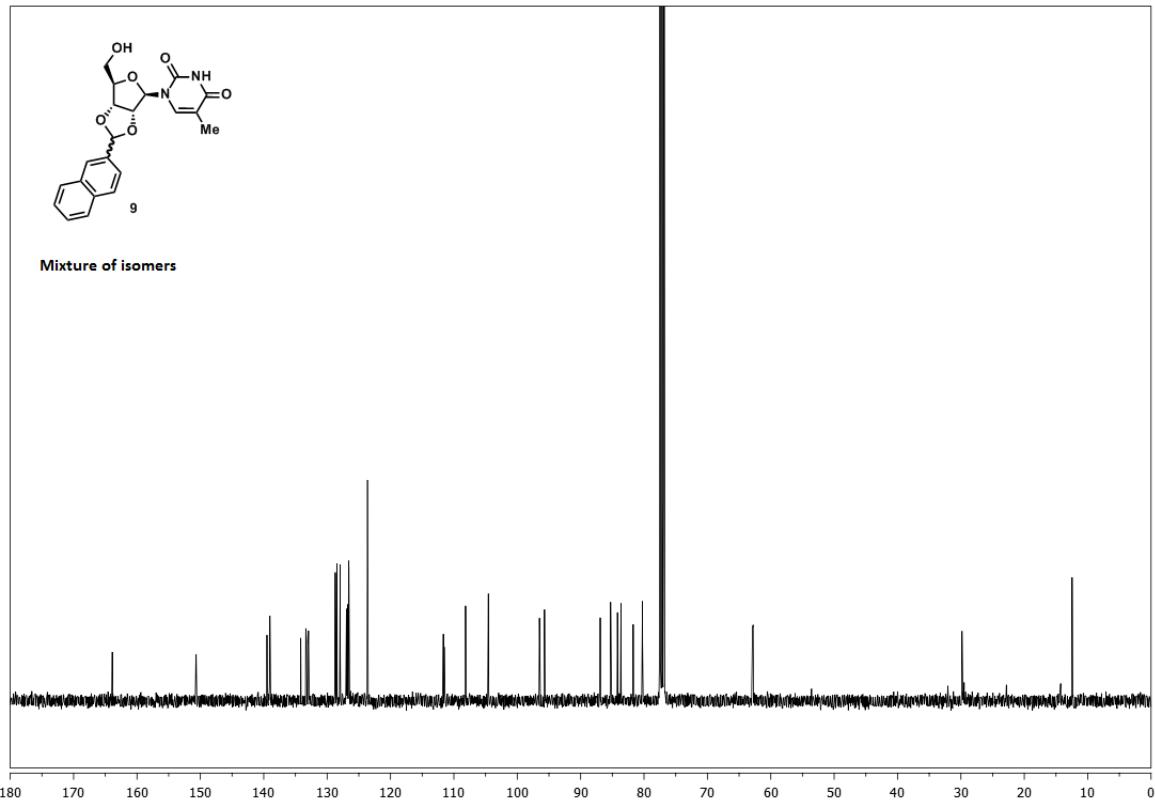
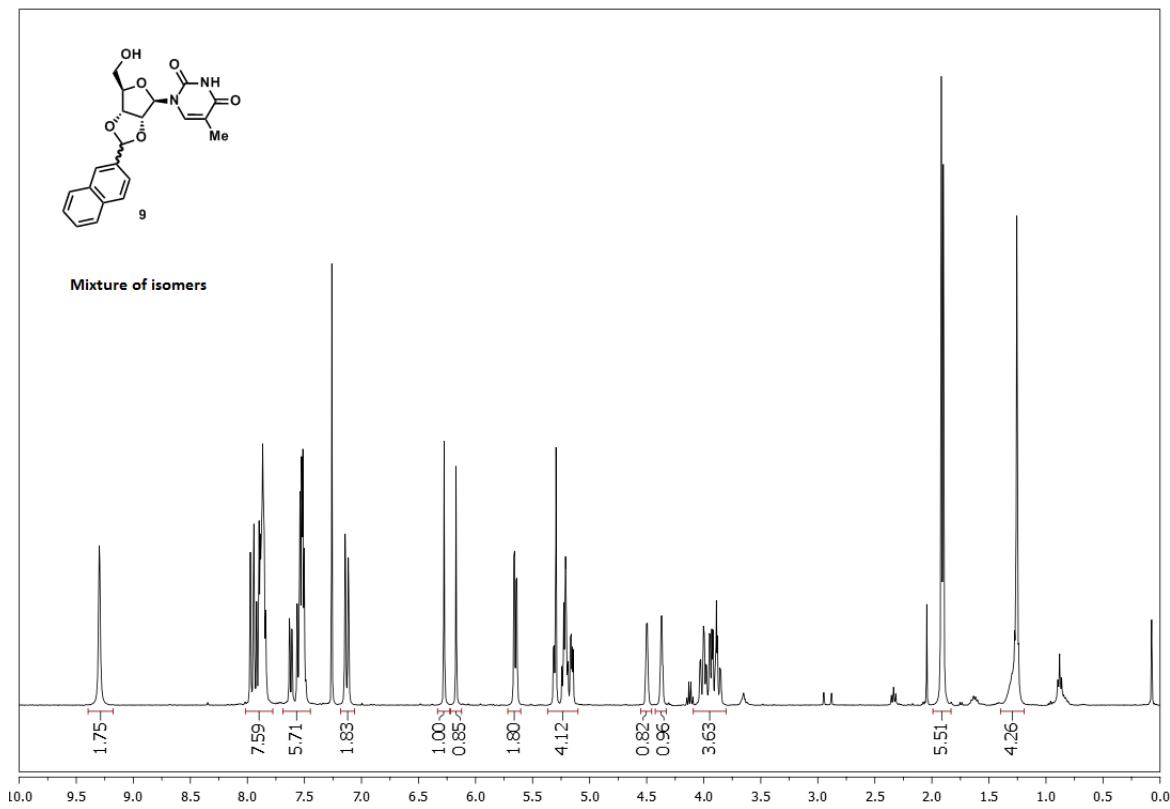
Mixture of isomers

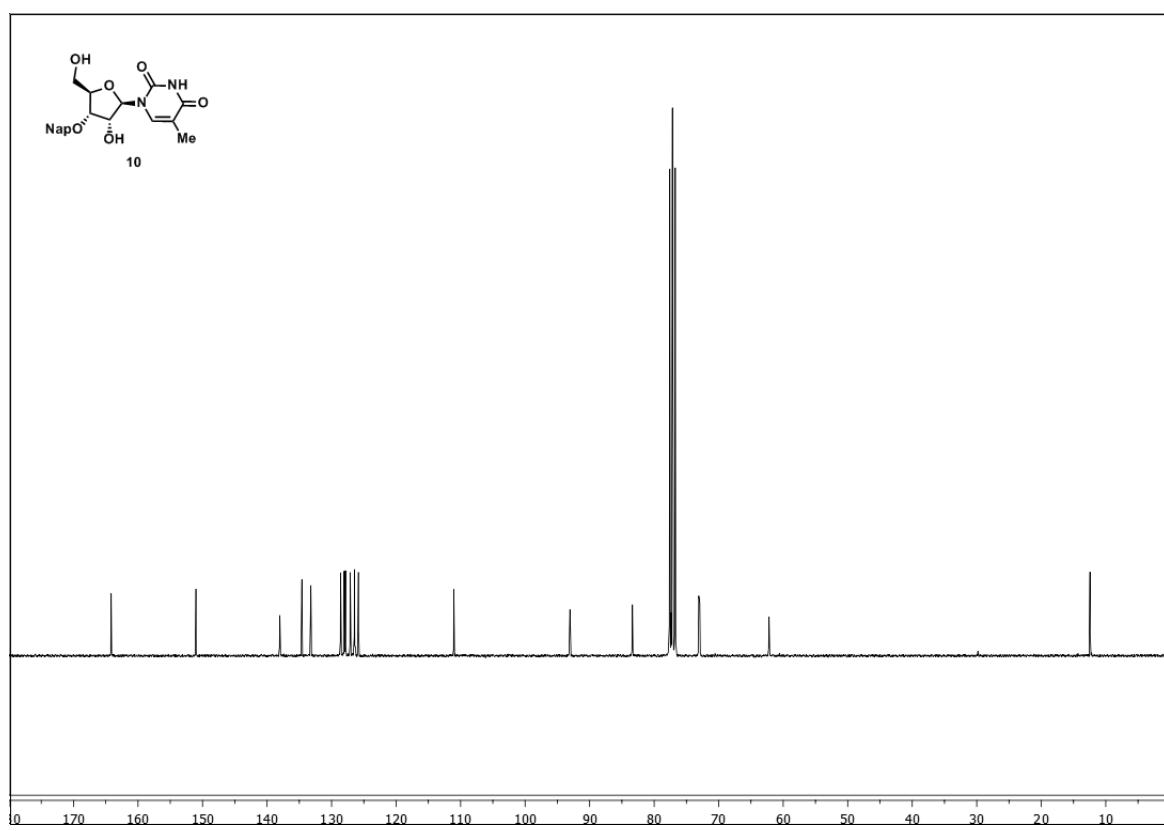
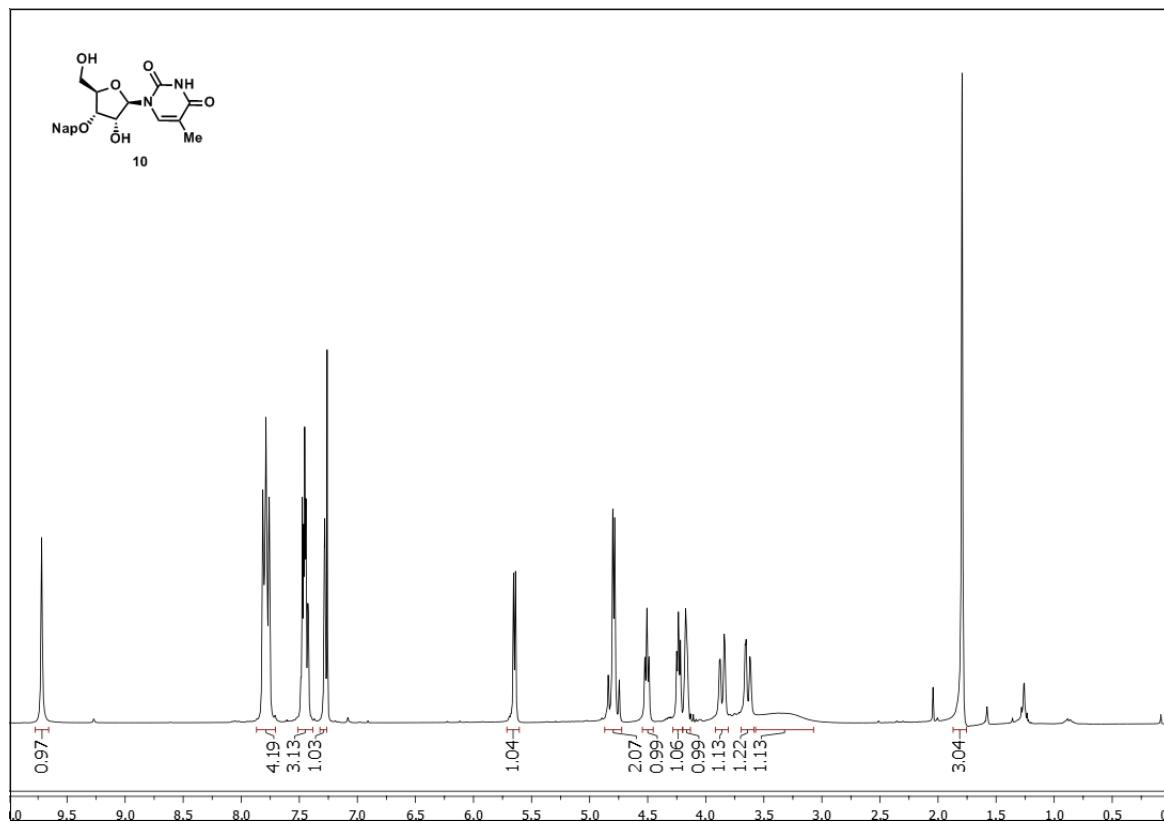


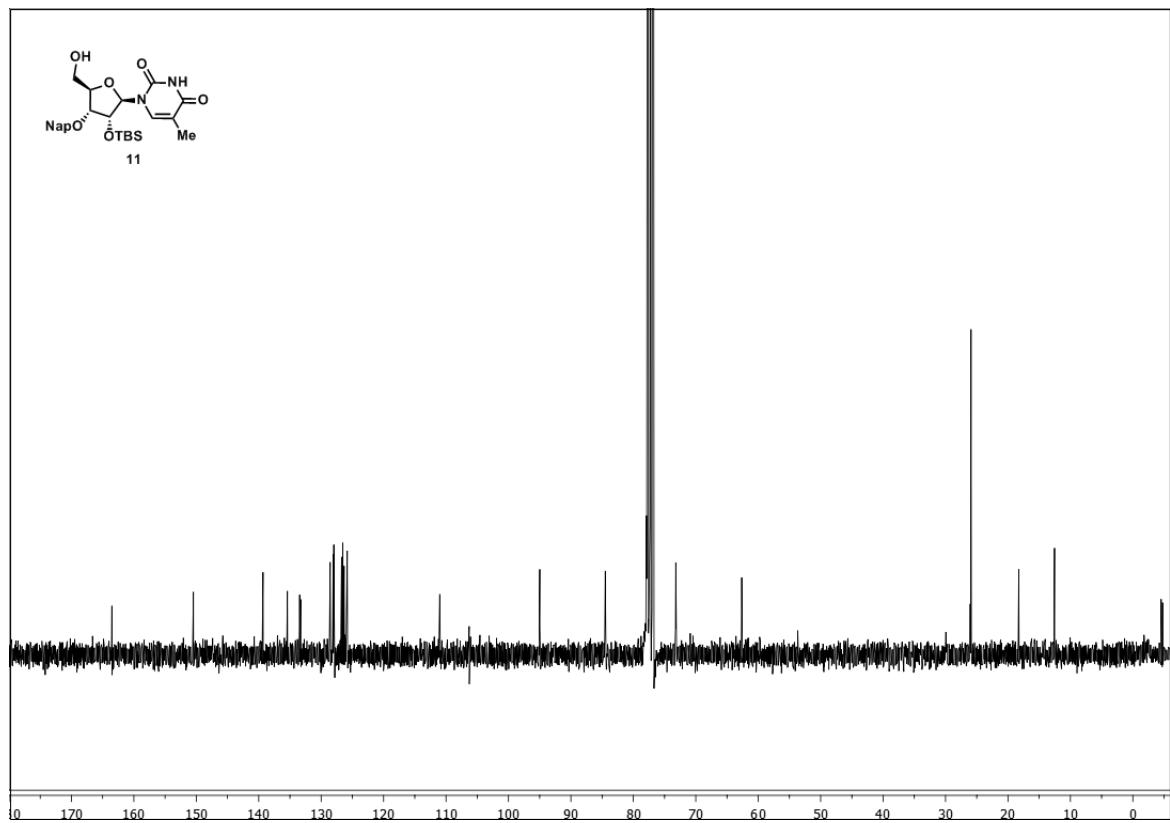
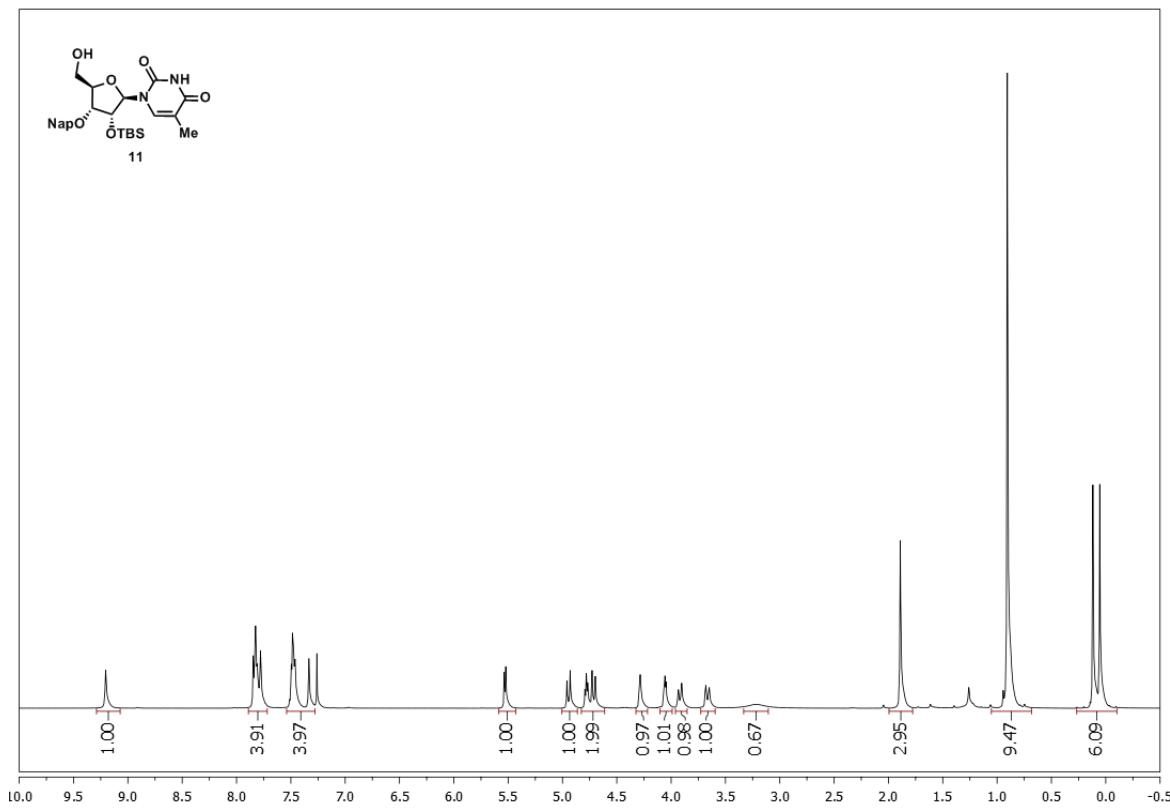
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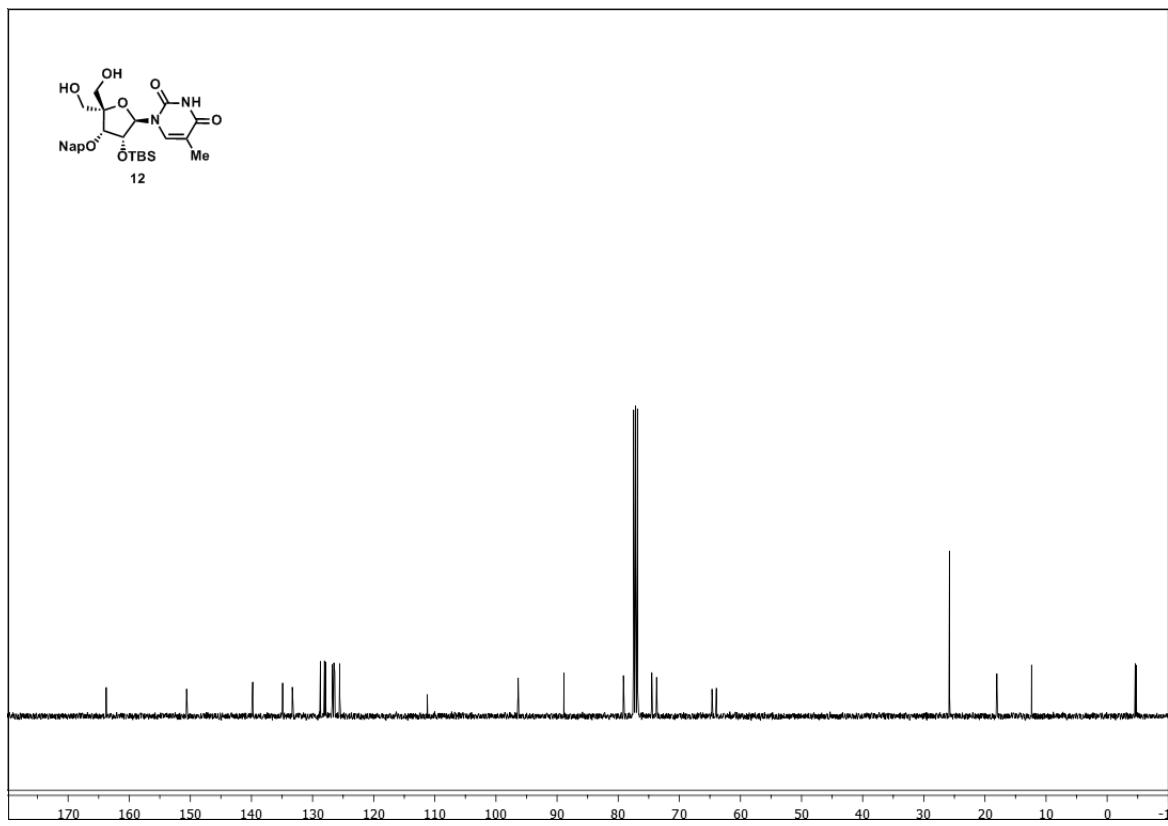
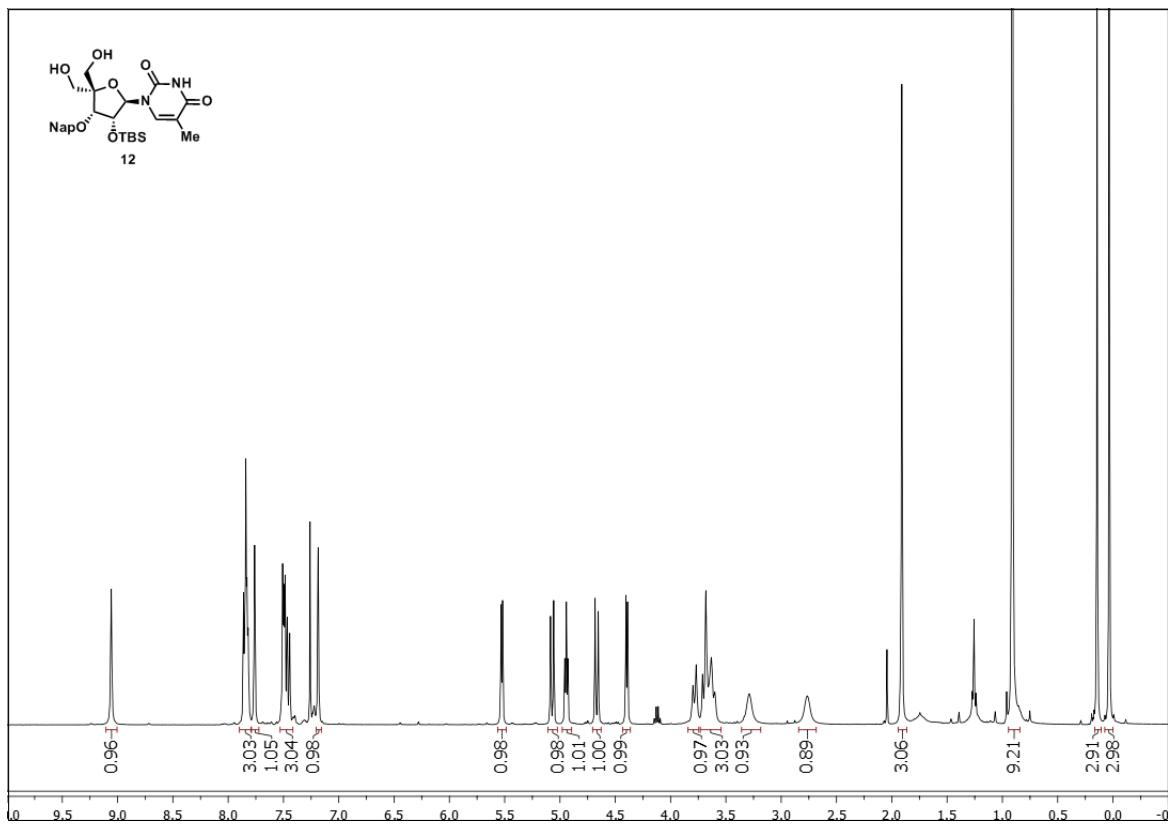


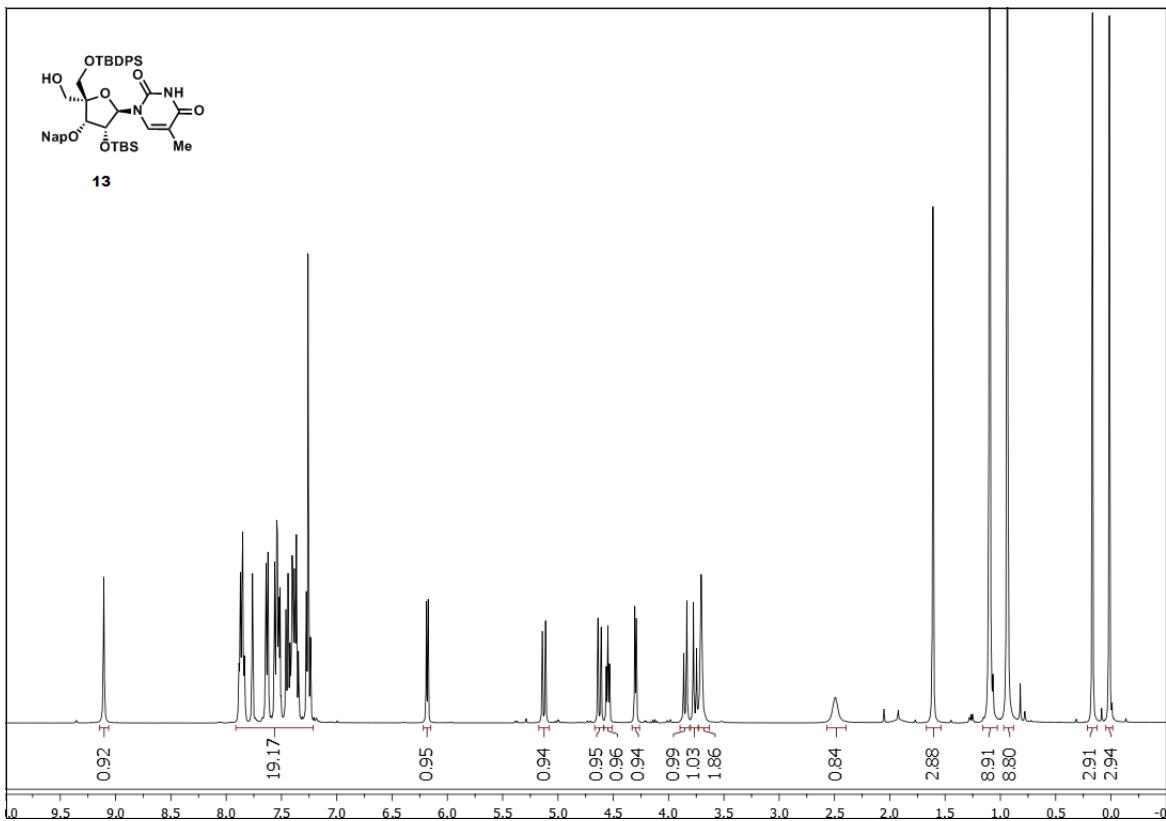
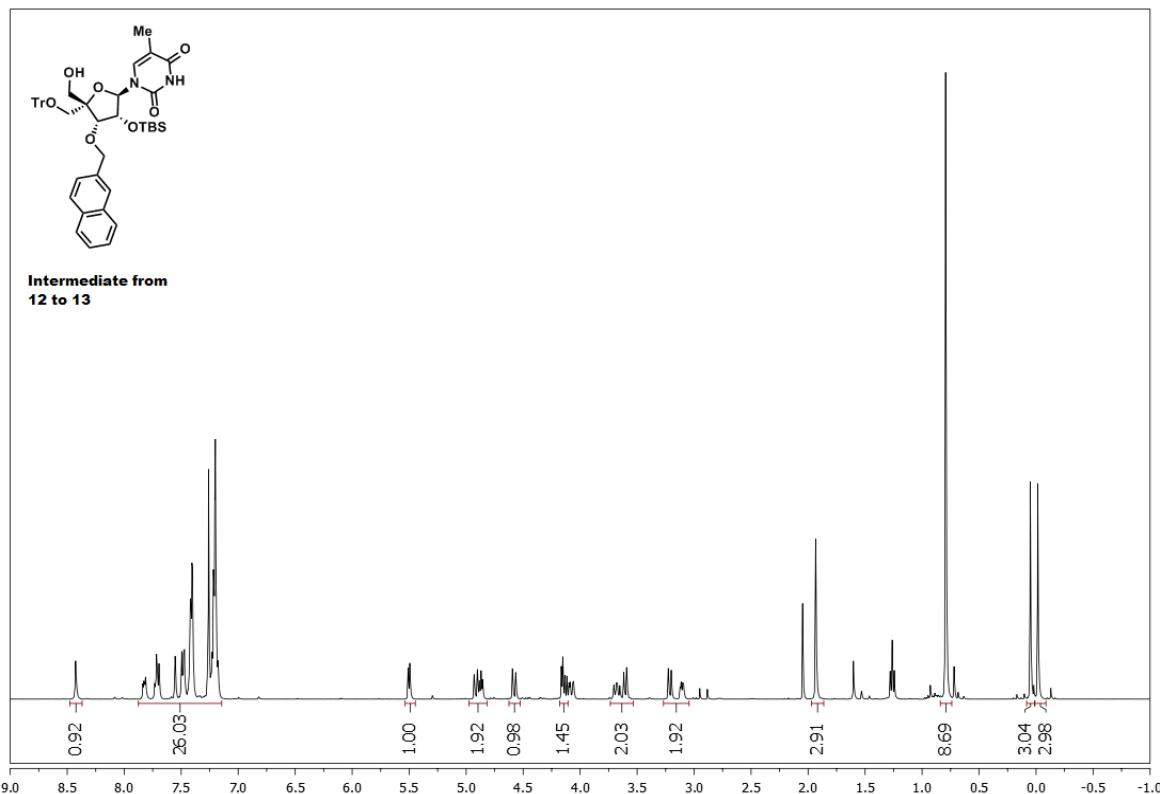


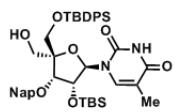




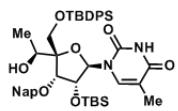
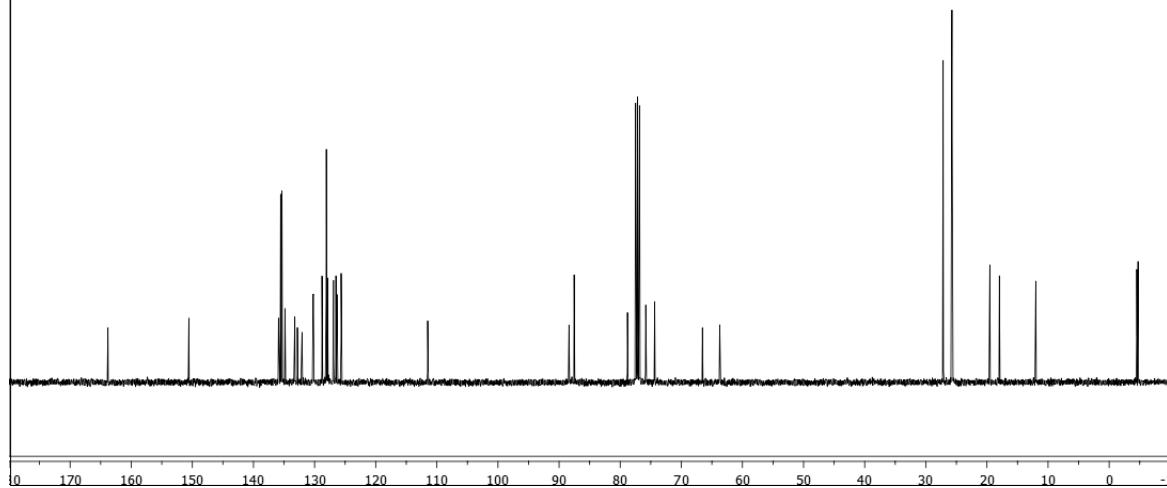




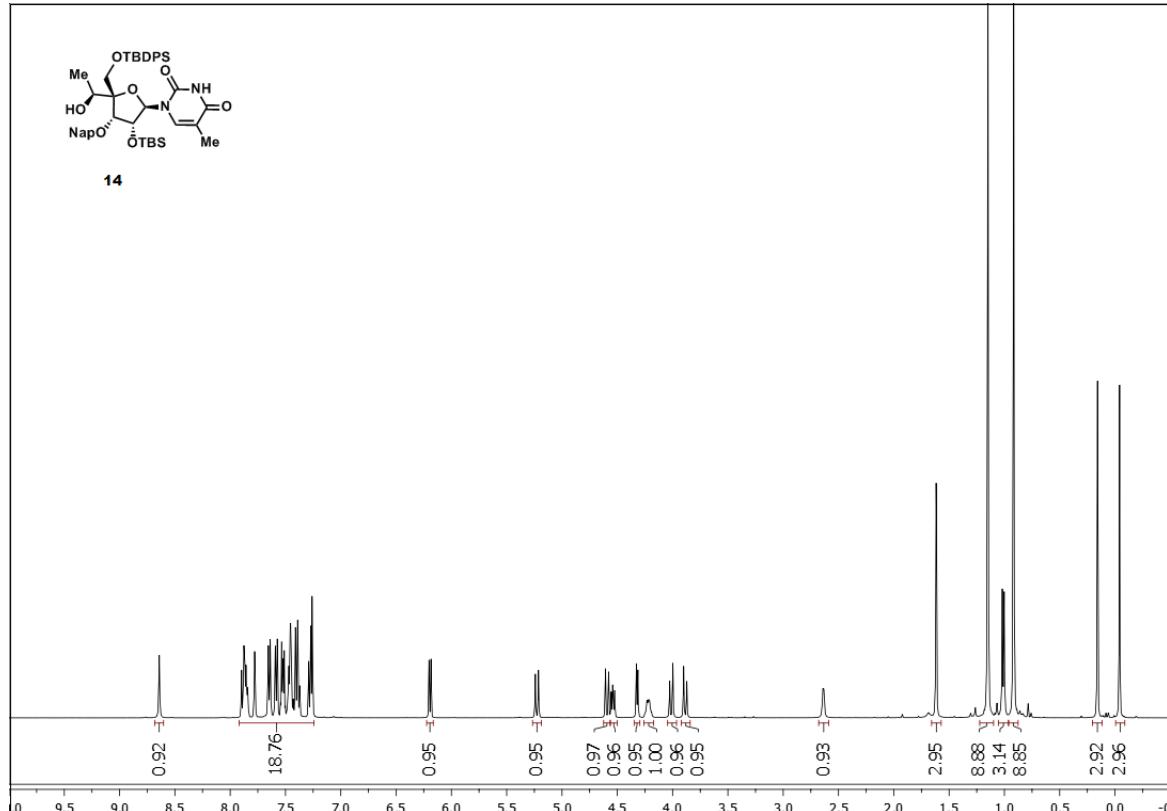


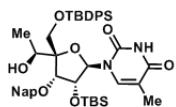


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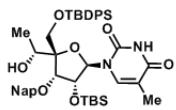
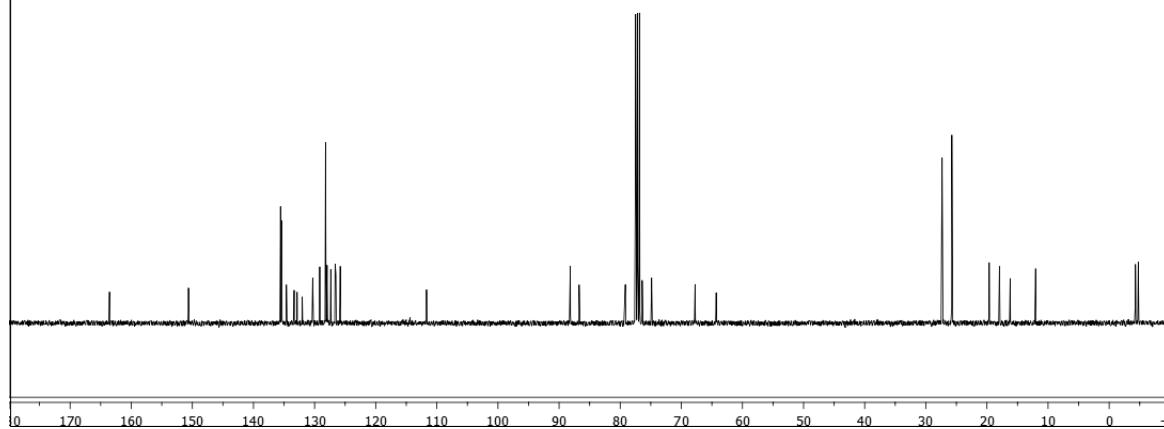


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14



15

Prepared from 14

Scheme 3.

k. DMP

l. LiAlH₄

